CDRH Learn; Process Validation

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Hello, my name is Joseph Tartal and I'm the Postmarket and Consumer Branch Chief in the Division of Industry and Consumer Education. There is a lot of great educational material available on quality systems, including how to design the right device so it will meet user needs, and how to qualify your suppliers so the products and services received meet your needs to manufacture that device. These efforts require your valuable resources, such as time and money. The last thing you want now is to have problems during manufacturing - such as device failures. This is where process validation comes into play. During my years in industry, I spent time performing process validation work, and it felt good to know that when done correctly, the manufactured devices were going to meet their predetermined specifications every time. At the end of the day, this is what you want, your customers want, and we at FDA want - working devices that meet specifications.

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By the time I'm finished, I want you to know the following learning objectives:

Understand the background and definitions in regards to process validation, such as where did process validation come from in the 1996 Regulation, and what are the key terms used.

Understanding these definitions is important so that everyone is using the same terms, and those terms are used correctly.

Recognize when process validation is required, and when it may be a good idea even if not required.

Understand the process validation regulatory requirements. These are the shalls and musts per the regulation. You have to do these.

Identify guidance and best practice information, such as Installation, Operational and Performance Qualifications.

Understand requirements for Process Monitoring, Process Changes and when to Re-validate. Once completed, process validation does not go into a file never to reviewed again. One thing I can guarantee is this: At some point, change will occur, so how do you plan to handle that change?

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The requirements for process validation can be found in 21 CFR 820, otherwise known as the Quality System Regulation, which was published in the Federal

Register in October 1996. Also, there was a lot of good discussion between the FDA and all stakeholders when the draft rule went out for public comment. These comments and the agency responses can be found in the preamble of the regulation, and are useful to review in order to understand the FDA's thinking at that time.

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First, I want to provide some background history on Process Validation. Process Validation is codified in the regulation under 21 CFR 820.75. It was not new to the 1996 Quality System Regulation. Parts of it came from the original 1978 medical device Good Manufacturing Practice regulation, or GMP. Lots of work was done regarding process validation during the 1970s, 80s, and 90s. After this presentation, please feel free to click on the hyperlink.

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Process Validation, like many other quality practices, has consistently evolved. The Global Harmonization Task Force, or GHTF, 2004 Guidance is the most current resource that addresses medical device process validation. As a reminder, guidances are voluntary and not mandatory. However, guidances often provide good suggestions, ideas, and recommendations on how to meet Agency requirements. The GHTF Guidance may be found at the International Medical Device Regulators Forum webpage in the GHTF archives, under Study Group Three. Here's a link to the Study Group Three webpage.

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Next, I want to mention that the quality system works together and is intertwined. It is not in separate silos. Design and design transfer will feed into production and process controls as well as process validation. Let's consider the example of Risk Analysis. You'll want to know the impact of risk on the manufacturing processes and specifications, especially for essential design outputs. Risk Analysis can help you to determine priorities and focus resources, even with processes and process validation. ISO 14971, a voluntary risk management standard can help and I have seen it used in industry for analyzing process risk.

Also, what is purchased - products and equipment - and their specifications, will affect your processes. For example, if there is a component and it is deemed an essential design output, you may request your supplier to perform process validation as part of your purchasing controls agreement.

Who you hire and how they are qualified or trained will impact your processes and process validation. And of course, production and process controls in

general will impact process validation. For example, the regulation requires under 21 CFR 820.70(i) that automated processes be validated.

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Now let's review several definitions as they relate to process validation, as I want to be clear on these terms. This is important when conversing in your own internal cross functional teams or when speaking with an investigator. Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

By objective evidence, I mean supporting the existence or truthfulness of it. Objective evidence may be an observation, a measurement or a test; for example I can measure an item on a scale to verify how much it weighs.

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Next, let's define validation. Validation means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled. Again, objective evidence that confirms requirements for first specific intended use, design validation and second can be consistently fulfilled, process validation; for design validation an example may be a clinical trial and the results and for process validation an example may be a process validation protocol and its results.

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Last, we'll look at Process Validation. It means establishing - define, document, implement or do it - by objective evidence that a process consistently produces a result or product that meets its predetermined specifications. It is reproducible and predictable, and gives me a known predetermined output. This is the end goal for process validation, as we know that manufacturers should not rely solely on inspection and testing to ensure that product is adequate.

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Now that we know what process validation means, when do we have to do it? Process validation is required when a process cannot be "fully verified" by subsequent inspection and test. "Fully Verified" means being able to confirm with high confidence all of the key quality attributes.

For example, if I'm performing an injection molding process, I need to look at all the molded pieces as well as all of their key quality attributes. These may be dimensional measurements which may be fully verifiable, and also strength specifications, which may require impact resistance testing which I cannot fully verify since it is destructive. Therefore, the process must be validated. Also, all

injection molding processes that I'm aware of are automated. This is another reason to validate, and injection molding is specifically noted in the preamble as a process that requires validation. However, you will need to make these determinations for your own processes.

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To further expand upon this, here are three other process examples and the thoughts behind why I believe they would or would not require validation. Please note these are examples and not absolutes, so you will need to characterize your own specific processes and their results.

Is validation required for a sterile package sealing process? The answer is yes - sterility requires process validation and the packaging process requires destructive "burst" testing.
What about the Dimensions of a Manual Cutting Process? In this case, likely not.

If I can measure all the dimensions and key quality attributes from every output, then I can fully verify the process. Also, the key word is "manual." We validate processes, whereas we qualify people. So if a person is manually performing the whole process, then the person is qualified through training.

And finally, let's consider the example of a Filling Process. This depends. Is the filling process automated or manual? Is it Aseptic? The preamble and the GHTF guidance provide some good examples as to when certain processes should be validated. Also, even if not required to validate, I may want to do so for other reasons, such as cost. I recommend reviewing the GHTF Guidance Decision Tree Figure One. It's a good tool to use. For example, you may have a process that can be fully verified, but the test is cost prohibitive. This is not an FDA concern, but it is your concern, and therefore, you may want to validate. According to 21 CFR 820.75, if the process cannot be fully verified, then you must validate.

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A natural question is when should you start your process validation? The answer is: the earlier the better. There are no requirements in design controls, but there are requirements under finished device acceptance activities that all activities must be completed prior to release. This includes the device master record requirements, such as process validation. Therefore, no finished device can be released into distribution until process validation activities are completed. As for when to begin, I suggest beginning process validation during design transfer so that you'll have actual manufacturing units for design validation. That's one

reason why it's good to have cross functional teams. Otherwise, you'll need to prove why the prototypes are equivalent to actual manufacturing units. Pragmatically, you can also start to address any issues that may arise from manufacturing scale-up, production facilities, capital equipment, identified process risk and potential changes.

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Master validation plans are not required in the quality system regulation. However, I highly recommend using a master validation plan as it helps you develop a road map for what needs to be done, how it will be done and who will do it. It's recommended in the GHTF guidance and it's considered a quality plan. Also, it becomes extremely important when you have multiple process and multiple process validations going on at the same time. For example, I once set up a manufacturing process in a clean room that needed to look at contamination controls, HVAC and air flow, water systems, gowning, and multiple manufacturing processes. The only way I could keep track of everything was by using a master validation plan.

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The requirement in the regulation is that you must have those approving the validation date and sign it, and include "where appropriate" the major equipment used. "Where appropriate" means it is appropriate unless you document a justified rationale for why it is not. For example, if I have a heat sealing process and I have multiple heat sealers, it's appropriate to identify each of them specifically.

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Those personnel performing validation work must be qualified to do so. This means they must be trained and qualified in the process, use of the equipment, and process validation. Personnel who perform verification and validation activities also need to know about defects that may be encountered. I'll use the heater sealing example again. Personnel performing the validation must be trained in the heat sealing process, including use of the heat sealer, and they must be aware of defects that may occur, such as not having a proper seal or any other defect.

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Please note that we validate processes and qualify all equipment used in the manufacturing processes. 21 CFR 820.70(g) states that you must ensure that all

the equipment used meets its specified requirements, and is designed, constructed, placed and installed correctly for its use.

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The GHTF guidance discusses this further and simply states that everything must be installed correctly. It provides items to consider, such as equipment design features, installation and environmental conditions, including ancillary systems such as electrical requirements. For example, with a heat sealer, is there an 110V or 220V electrical outlet requirement? Is there enough space in the room if it requires cooling? Also, safety features and supplier documents, such as equipment manuals and more, are noted for consideration. In the end, for installation qualification, be sure that your equipment is installed correctly and is capable of doing what you need it to do.

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Now I want to discuss operational qualification or OQ. Here you want to challenge your process and its parameters in order to understand and characterize it. You want to know its capabilities, its capacity, and its ranges. You want to determine your process control limits, material specifications, process change control and training needs. It is an experimental phase and you can see worst case scenarios, including running to device failure. Just make sure the resulting product is quarantined. You want to see how far you can push your processes. If you previously conducted a process risk analysis, such as Failure Mode Event Analysis, then test that analysis. See if the results match the initial analysis. Then update your risk analysis accordingly. Perform verification and validation for any software used in the process.

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Operational Qualification is a time to understand your manufacturing processes, including how process inputs impact process outputs, and how they relate to specified criteria and limits. The time you invest upfront to understand these parameter and their impacts will pay off later on.

For example, in the heat sealing process, what interactions among different parameter settings affect the seals output? If I change the temperature, pressure and time, what does it do to the seal thickness and strength? If these are set too high, they may damage the materials and equipment. If they're set too low, there's not a proper seal. What happens when these are changed? How does it affect process outputs? I want to know this in order to set the most appropriate process parameters settings.

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Once you verify output that your product meets specification when manufacturing within established operating limits set in your operational qualification, you will move on to performance qualification, or PQ. In PQ we do not expect failure. It builds off the work done in OQ and continues to look at measureable attributes for continuous monitoring. Use the approved documented procedures that will be used by all the trained and qualified manufacturing staff. Perform it under anticipated normal manufacturing operations. It's a good idea to cover multiple operators, lines and shifts, if you have more than one. I've noticed for overnight shifts that it's always interesting to see what happens differently compared to the day shift. You do not want differences in performance. Instead, you want things to operate the same on all shifts, night or day, and regardless of operator. Also, you should consider possible factors that result in longer-term variation, such as seasonal changes in humidity, which is an issue in certain regions like the southern United States. The goal is to ensure the process is repeatable and stable long term.

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How many runs and samples are needed, and at what frequency? You determine it. What I can say is three is no longer the magic number. I understand it once was, and was even debated in the regulation. I remember using three back in the mid-1990s, but today you should determine the number of runs using a rationale such as a statistical significance. You determine it, and support your rationale. For example, if you use a percent confidence then you must understand what that means for the process, and why that statistical tool was utilized. Run Length, Sample size, Frequency and Duration need to be defined and understood when used. The GHTF guidance says it should be repeated enough to assure that the results are meaningful and consistent.

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If things go well and you have a controlled process, you will build upon each aspect of the validation and zero in as it moves forward. The IQ will provide your equipment capabilities, the OQ your operational limits, as identified from the challenge conditions, and then PQ, in the center, with your nominal operating settings. This is what you want, and this leads to a stable and capable process. Stable means you get the same results over and over. Capable means those reproducible results fit with its remaining variation into your specifications. This is what gives you confidence that the process with known inputs will give you

predictable and predetermined outputs. These may be materials, components or finished devices. Unfortunately, not all processes work out this easily. Sometimes you may have to redesign the process, and other times you may even have a known rate of failure. When this is the case, be able to control and explain it. Also, know how your monitoring, inspecting and testing relate back to your device risk and the risk benefit determinations identified.

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Does this mean we are now done, to never to look at the process again? No. You still have to monitor it over time. Now, if you've done OQ correctly, then you already know the important measurements to monitor. And if you've done PQ correctly, you know their frequency with regards to every day operations. The regulation states you must establish procedures for monitoring and control to ensure that specified requirement continue to be met. The proper monitoring is important, as it will identify and detect changes over time.

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The process validation monitoring will take into consideration how robust the process is. If the process is influenced by some variation, thereby making it not fully capable, then it will likely require more monitoring. You may also want to use statistical process controls to look at deviation and percent confidence. Also, controls charts and action limits can be established and used. For example, action limits for seal temperature can be set prior to device specification failure. As the results are monitored, adjust the temperature and monitor the process before specification failure occurs. As time goes on, and your process is stable, always meeting your target, you may decrease the frequency of monitoring. But you determine that.

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Production and process changes -- One thing I can tell you, it is not a matter of if but when you will have process changes. When you make changes to specifications, methods or process, equipment and materials, you have to see if those changes now require verification or validation, where appropriate. The verification or validation must be done prior to implementation of the change. This may prompt a new validation or, if previously validated, require re-validation.

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Re-validation -- when changes to a process or deviation occur, the manufacturer must review and evaluate the process and perform re-validation where

appropriate. Changes to processes as we just discussed, or process deviations such as an increase towards action limits or failures, for example, a decrease in seal strength or open seals from the heat sealing, then the process must be evaluated and re-validated unless there is a documented justification as to why it is not needed.

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Here is a list of additional examples of revalidation:
Changes to the actual process, such as a new heat sealer or piece of equipment.
Negative trends. For example, monitoring shows that the sealer is running hot and trending higher.
Product design changes, like a new pouch packaging material that could have an effect on the sealing process and finished device.
Even moving the equipment from one part of facility to another may require revalidation.
Also, for re-validation, maybe just part or the entire original validation needs to be completed again. That is for you to determine. Just make sure to document and justify why.

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Historical data, information and data from device history records such as batch records, control charts and inspection can be used. I'll let you know that quantitative data is generally more useful than qualitative. Also, the historical data does not usually give you a complete picture. So while useful, by itself, it will likely not be enough. However, historical data can be used for any validation.

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Thank you for your time and in summary, I ask that you take on the following call to actions:
Understand your legal obligations for process validation. Use the GHTS guidance as a voluntary tool to meet those obligations. Perform process validation to ensure that predictable and predetermined outputs are always the case, and specifications are always met.

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This presentation and other helpful videos and educational resources can be found at CDRH Learn. For text- based information on premarket and post market topics, including how to bring a medical device to market, please visit Device Advice. For additional information on these or any other medical device regulatory topics, feel free to call us at the Division of Industry and Consumer

Education by phone or email - our contact information is listed on this slide.
Thanks for watching.